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Prevalence and determinants of elevated high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy

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ABSTRACT

Background: This study was designed to evaluate the prevalence and determinants of increased high-sensitivity cardiac troponin T (hs-cTnT) as a marker of cardiac injury in patients with hypertrophic cardiomyopathy (HCM).
Methods: A total of 98 consecutive patients with HCM (71.4% males; mean age 51.18 ± 15.47 years) between 2012 and 2013 were evaluated by measuring the level of serum hs-cTnT along with other clinical assessments.
Results: There were 42 (42.9%) patients with a minimum serum hs-cTnT level of 14 ng/L. The mean hs-cTnT level was 12.37 ng/L (6.94–24.26 ng/L). There were significant differences in chest pain New York Heart Association functional class, left ventricular hypertrophy in the surface electrocardiogram, non-sustained ventricular tachycardia in 24-h electrocardiogram-Holter monitoring, left atrial (LA) area index, ratio of peak early (E) transmitral filling velocity to peak early diastolic annular velocity (Ea septal) at the level of the septal mitral annulus (E/Ea septal), maximum left ventricular (LV) wall thickness ≥ 30 mm, and peak LV outflow gradient ≥ 30 mmHg in echocardiography between the patients with hs-cTnT < 14 ng/L and those with hs-cTnT ≥ 14 ng/L. However, after multivariate analysis, age, maximum LV wall thickness, LA area index, and E/Ea septal remained as the independent determinants of elevated hs-cTnT in HCM.
Conclusions: The results demonstrated that hs-cTnT was elevated in a significant number of our HCM patients; therefore, hs-cTnT can be introduced as a valuable marker of myocardial injury in HCM patients.

Introduction

Hypertrophic cardiomyopathy (HCM) has been generally defined as an unexplained hypertrophied non-dilated left ventricle in the absence of any other cardiac or systemic disease [1]. Alongside a marked heterogeneity in clinical expression and prognosis, unexpected sudden cardiac death in all ages, especially young people, is the most important component of its natural history, rendering HCM a dilemma to clinicians and cardiovascular specialists. Other complications linked to higher mortality or morbidity in HCM are progressive heart failure and atrial fibrillation (AF), leading to embolic stroke [2,3]. However, despite the different markers that are associated with myocardial ischemia and injury, there are only a few reliable biomarkers for the clinical assessment and prediction of events in HCM patients. In this regard, high-sensitivity cardiac troponin T (hs-cTnT) might be useful for risk stratification and predicting adverse cardiovascular events in HCM patients.

Cardiac troponin and its certain subtypes are currently the markers of choice because of their tissue specificity and sensitivity. Serum concentration of hs-cTnT is a novel and highly sensitive and specific marker of myocyte injury and can detect concentrations significantly lower than 99th percentile of the normal reference population [2,4]. Indeed, hs-cTnT is a reliable indicator of subclinical or ongoing myocardial damage. Nevertheless, there are several conditions other than acute myocardial infarction which could result in elevated hs-cTnT levels. These properties of hs-cTnT have prompted endeavors to seek more optimal screening or management of different myocardial problems [4,5] and HCM should be regarded as a differential diagnosis in patients with raised hs-cTnT in the absence of coronary artery stenosis.

Given the relative paucity of data on the prevalence and determinants of increased hs-cTnT in HCM, we aimed to evaluate this marker of cardiac injury in patients with HCM.

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Methods

One hundred ten consecutive patients, who had established HCM diagnosis and were admitted between 2012 and 2013 to the Outpatient Clinic of Tehran Heart Center, were included in the present study. All patients were clinically evaluated for ischemic heart disease, of which sixty-five were suspected to have coronary artery disease (CAD) and underwent coronary angiography. Finally, 12 patients were excluded because of evidence of significant CAD in coronary angiography. The patients were evaluated through medical history, clinical examination, 12-lead electrocardiography (ECG), M-mode and two-dimensional Doppler echocardiography performed by an experienced echocardiographer, and 24-h ECG-Holter monitoring on the same day. The exclusion criteria consisted of recent established acute coronary syndrome, creatinine > 1.5 mg/dL, and evidence of ischemic heart disease.

Variables in medical history included gender, age, dyspnea, exertional chest pain, cigarette smoking, diabetes, hypertension, hyperlipidemia, history of syncope and aborted sudden cardiac death, and family history of HCM or sudden cardiac death. Recorded findings of the ECG comprised AF, left ventricular hypertrophy (LVH) based on the precordial voltage criteria of Sokolow and Lyon [6], pathologic Q-wave (≥0.04 s duration), and QRS duration. Additionally, 24-h ECG-Holter monitoring was performed to register non-sustained ventricular tachycardia (NSVT), defined as three or more beats ≥120 bpm on ambulatory (Holter) ECG. Echocardiographic parameters comprised left ventricular ejection fraction (LVEF), left atrial (LA) area, maximum LV wall thickness, left ventricular outflow tract (LVOT) gradient, E-wave, and E/Ea septal (see below). LVEF was determined from apical two-chamber and four-chamber views via the Simpson biplane method. Systolic dysfunction was defined as LVEF below a cut-off point of 50%. LA area was measured by planimetry using apical four-chamber view and was indexed to the body surface area. LVOT gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation with a cut-off point ≥30 mmHg at rest. Peak early (E) transmitral filling velocity and peak early diastolic annular velocity at the level of the septal mitral annulus (E/Ea septal) were measured, and E/Ea septal ratio was calculated. The criteria for the diagnosis of HCM were LV wall thickness ≥15 mm without any other cardiac or systemic disease capable of begetting LVH [1]. Based on the morphologic and hemodynamic findings in echocardiography, HCM was classified into the three subgroups of (1) HCM with obstruction (presence of a basal LVOT obstruction gradient ≥30 mmHg at rest), (2) HCM without obstruction, and (3) apical HCM characterized as hypertrophy predominantly involving the LV apex on echocardiography and giant negative T waves on the ECG.

In order to evaluate the serum hs-cTnT level and its association with clinical factors, the patients were divided into two groups: those with a serum hs-cTnT level < 14 ng/L and those with a serum hs-cTnT level ≥14 ng/L.

Blood samples were collected at the time of clinical evaluation. The test was repeated 24 h later in the patients having attended for 24-h ECG-Holter monitoring ($n = 73$). There was no significant difference between the two values (correlation = 99.4%), and the first value for hs-cTnT was used for analysis. The plasma samples were centrifuged at 15 000 rpm for 10 min. Serum levels of hs-cTnT were assayed with the Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland) using electrochemiluminescence according to the manufacturers' instructions. The inter-assay variations for the determination of normal and abnormally high levels of hs-cTnT were 5.3% and 2.4%, respectively, and the intra-assay variations for the determination of normal and abnormally high levels of hs-cTnT were 3.6% and 2.2%, respectively, with a lower detection limit of 3 ng/L. The cut-off value for hs-cTnT by a reference interval of 99% was 14 ng/L.

Informed consent was obtained from all the patients, and the study was approved by the Ethics Committee of Tehran Heart Center and the Committee of Medical Ethics of Tehran University of Medical Sciences.

The continuous variables are expressed as mean ± standard deviation or median (interquartile range), and they were compared between the patients with hs-cTnT ≥14 ng/L and those with hs-cTnT < 14 ng/L using the Student *t*-test or the Mann–Whitney *U* test. The categorical variables are presented as frequencies and percentages, and they were compared between the two above-mentioned groups (hs-cTnT ≥14 ng/L vs. hs-cTnT <14 ng/L) using the chi-square or the Fisher exact test. The multiple logistic regression model with the backward elimination method was employed to determine the predictors of elevated hs-cTnT (≥14 ng/L).

Variables with a *p*-value less than 0.2 in the univariate analysis were included in the multivariable model. The effects of the independent predictors of elevated hs-cTnT in the final model were expressed as odds ratios (OR) with 95% confidence intervals. Model calibration was estimated using the Hosmer–Lemeshow goodness-of-fit statistic (p-value = 0.851). Model discrimination was measured using the c statistic, which is equal to the area under the ROC (Receiver Operating Characteristic) curve. The statistical software SPSS (version 15.0) for Windows (SPSS Inc., Chicago, IL, USA) was used.

Results

Having excluded 12 patients with evidence of CAD, we studied 98 eligible patients, comprising 70 (71.4%) males and 28 (28.6%) females with a mean age of 51.18 ± 15.47 years. There were 42 (42.9%) patients with serum hs-cTnT levels of ≥14 ng/L. The median for the hs-cTnT level was 12.37 ng/L (6.94–24.26 ng/L). There were 6 patients with hs-cTnT levels below the detection limit of 3 ng/L; two of these patients had apical HCM.

The baseline demographic and echocardiographic characteristics of the participants are depicted in Table 1. The frequency of hs-cTnT ≥ 14 ng/L among the patients with a history of cigarette smoking was 7.1%, as opposed to 21.4% in the patients with hs-cTnT < 14 ng/L ($p = 0.052$). The frequency of hs-cTnT ≥ 14 ng/L in the patients with a diabetes history was 11.9%, in comparison with 8.9% in those with hs-cTnT < 14 ng/L ($p = 0.741$). Also, the frequency of hs-cTnT ≥ 14 ng/L was 21.45% in the patients with hyperlipidemia, in comparison to 14.3% in those with hs-cTnT < 14 ng/L ($p = 0.355$).

The univariate association between the variables and the serum level of hs-cTnT is summarized in Table 2. The serum hs-cTnT values were not significantly different between the patients with exertional dyspnea with different NYHA functional classes ($p = 0.247$). There was a low association between hs-cTnT values and AF ($p = 0.098$). Among the patients with a history of syncope, 43.47% had serum hs-cTnT levels ≥ 14 ng/L ($p = 0.945$). Sixteen (57.14%) patients with a family history of sudden cardiac death exhibited abnormal hs-cTnT levels ($p = 0.071$). In 70.0% of the patients with NSVT on 24-h ECG-Holter monitoring, the hs-cTnT level was ≥14 ng/L ($p = 0.003$). A number of patients ($n = 25$) did not agree to undergo ECG-Holter monitoring. Among the patients with significant LV wall thickness ≥30 mm, 62.5% showed hs-cTnT ≥14 ng/L ($p = 0.083$).

No significant difference was found between the subtypes of apical HCM, hypertrophic obstructive cardiomyopathy, and HCM without obstruction and abnormal hs-cTnT levels ($p = 0.151$). There were significant differences in chest pain NYHA functional class, LVH in the ECG, NSVT in 24-h ECG-Holter monitoring, LA area index, maximum LV wall thickness ≥30 mm, and peak LVOT

Table 1
Demographic data of the study population.

Variables	Patients ($n=98$)
Gender: male	70 (71.4%)
Age, years	51.18 ± 15.47
Dyspnea on exertion (NYHA)	
FC I	28 (28.6%)
FC II	61 (62.2%)
FC III	9 (9.2%)
Chest pain on exertion (NYHA)	
FC I	65 (66.3%)
FC II	28 (28.6%)
FC III	5 (5.1%)
Syncope history	23 (23.5%)
Aborted SCD	1 (1%)
Family history of HCM	39 (39.8%)
Family history of SCD	28 (28.6%)
hs-cTnT (ng/L)	12.37 (6.94–24.26)
hs-cTnT ≥ 14 ng/L	42 (42.9%)
ECG	
LVH	72 (73.5%)
Q Wave	19 (19.4%)
QRS Duration	108.00 (94.00–128.00)
AF	6 (6.1%)
Twenty-four-hour ECG-Holter monitoring ($n=73$)	
NSVT	20 (27.4%)
Echocardiography	
EF (%)	60.00 (55.00–60.00)
Apical HCM	7 (7.1%)
HOCM	21 (21.4%)
HCM without obstruction	70 (71.42%)
Maximum LV wall thickness (≥30 mm)	16 (16.3%)
LA area index	11.78 (10.69–14.84)
MR Severity	
Mild	55 (59.1%)
Moderate	18 (19.4%)
Severe	8 (8.7%)
Peak LVOT gradient at rest (≥30 mmHg)	22 (22.4%)
E/Ea septal	17.68 (12.56–25.15)

AF, atrial fibrillation; ECG, electrocardiography; EF, ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; FC, functional class; HCM, hypertrophic cardiomyopathy; hs-cTnT, high-sensitivity cardiac troponin T; LA, left atrium; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MR, mitral regurgitation; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.
Data are shown as numbers (percent), mean ± SD, or medians (Inter Quartile Range). Cut-off point for hs-cTnT = 14 ng/L.

Table 2
Univariate association between variables and serum levels of hs-cTnT.

Variable	hs-cTnT($n=56$) < 14 ng/L	hs-cTnT ($n=42$) ≥14 ng/L	p-Value
Male ($n=70$)	41 (73.2%)	29 (69.0%)	0.651
Female ($n=28$)	15 (26.8%)	13 (31.0%)	0.052
Age (years)	49.05 ± 14.49	54.02 ± 16.44	0.116
Dyspnea (NYHA)			0.861
FC I ($n=28$)	16 (28.6%)	12 (28.6%)	
FC II ($n=61$)	34 (60.7%)	27 (64.3%)	
FC III ($n=9$)	6 (10.7%)	3 (7.1%)	
Chest pain (NYHA)			0.043
FC I ($n=65$)	39 (69.6%)	26 (61.9%)	
FC II ($n=28$)	12 (21.4%)	16 (38.1%)	
FC III ($n=5$)	5 (8.9%)	0 (0.0%)	
Syncope history	13 (23.2%)	10 (23.8%)	0.945
Aborted SCD	1 (1.8%)	0 (0.0%)	0.999
Family history of SCD	12 (21.4%)	16 (38.1%)	0.071
ECG			
LVH	36 (64.3%)	36 (85.7%)	0.017
Q wave	9 (16.15%)	10 (23.8%)	0.388
QRS duration	111.37 ± 24.75	117.20 ± 29.91	0.325
AF	1 (1.8%)	5 (11.9%)	0.081
Twenty-four-hour 24-hour ECG-Holter monitoring ($n=73$)			
NSVT	6 (14.3%)	14 (45.25%)	0.003
Echocardiography			
EF (%)	57.39 ± 7.36	58.07 ± 7.07	0.621
Apical HCM	6 (10.7%)	1 (2.4%)	0.233
HOCM	9 (16.1%)	12 (28.6%)	0.136
HCM without obstruction			
LA area index	11.88 ± 2.36	13.83 ± 2.89	0.001
Maximum LV wall thickness (≥30)	20.55 ± 6.88	24.90 ± 6.79	0.002
MR severity ($n=93$)			0.281
Mild	32 (61.4%)	23 (56.1%)	
Moderate	7 (13.5%)	11 (26.8%)	
Severe	4 (7.7%)	4 (9.8%)	
Peak LVOT gradient (≥30 mmHg)	19.10 ± 30.03	26.35 ± 28.14	0.024
E/Ea septal	17.63 ± 8.95	25.75 ± 15.44	0.001

AF, atrial fibrillation; ECG, electrocardiography; EF, ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; FC, functional class; HCM, hypertrophic cardiomyopathy; hs-cTnT, high-sensitivity cardiac troponin T; LA, left atrium; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MR, mitral regurgitation; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.

gradient ≥30 mmHg between the two groups of patients with hs-cTnT < 14 ng/L and those with hs-cTnT ≥ 14 ng/L (Table 2). Finally, age, maximum LV wall thickness, LA area index, and E/Ea septal were determined as the independent predictors of elevated hs-cTnT in HCM (Table 3).

Discussion

In the present study, we assessed the prevalence and determinants of elevated hs-cTnT in patients with HCM. This assessment revealed that a significant number of our HCM patients (42.9%) had increased levels of hs-cTnT (≥14 ng/L). In addition, age, LA area index, maximum LV wall thickness, and E/Ea septal were the independent determinants of elevated hs-cTnT.

Cardiac troponins are sensitive and specific biomarkers for the diagnosis of acute myocardial infarction. Today, hs-cTnT serum concentration is a novel and highly sensitive and specific marker for the detection of concentrations significantly lower than 99th percentile of the normal reference population [2,4]. There are, however, several conditions other than myocardial infarction which can lead to troponin release; these conditions are attributed to myocardial injury. It is, therefore, important to distinguish acute causes of cTn elevation (e.g. acute myocardial infarction) from chronic elevations [7]. We found that hs-cTnT was elevated in a significant portion of our patients, who were diagnosed with HCM with no evidence of CAD, and there was no significant change in these values when the measurements were repeated after 24 h. This chronic elevation of hs-cTnT in stable HCM patients may help to identify a larger number of HCM patients with ongoing myocyte injury.

There are only a few studies in the existing literature that have reported increased levels of cTn in patients with HCM [8–10]. Moreno et al. [10] showed high levels of hs-cTnT in up to 42% of stable HCM patients; these levels were higher than those in the control group but relatively lower than the values in acute coronary events. Likewise, we found that 42.9% of our patients had increased hs-cTnT levels.

Table 3
Multivariable predictors of the serum level of hs-cTnT.

Variable	Odds ratio (95% confidence interval)	p-Value
Age	1.071 (1.021–1.123)	0.005
LA area index	1.188 (0.972–1.453)	0.093
Maximum LV thickness	1.184 (1.049–1.337)	0.006
E/Ea septal	1.046 (0.994–1.100)	0.083

Hosmer–Lemeshow goodness-of-fit statistics = 4.071; degree of freedom = 8; $p=0.851$; logistic regression analyses ($n=98$ patients). Cut-off point for hs-cTnT was 14 ng/L. Area under the curve: 0.840 (0.758–0.921); $p=0.001$.
hs-cTnT, high-sensitivity cardiac troponin T; LA, left atrium; LV, left ventricular.

Maximum LV wall thickness, as an important marker associated with sudden cardiac death and LV systolic dysfunction deterioration in HCM [11–13], had a significant association with cardiac troponin I (cTnI) and hs-cTnT levels in two previous studies [10,13]. We also found a significant association between maximum LV wall thickness and hs-cTnT levels in our multivariate analyses.

A major pathophysiologic abnormality in HCM is diastolic dysfunction, which can be assessed by LA size or E/Ea septal. LA remodeling is allied to greater LV hypertrophy, more diastolic dysfunction, higher filling pressures, and higher risk of atrial arrhythmias [14]. In the Kubo et al. study [13], an independent association between cTnI and E/Ea septal was reported. Moreno et al. [10] also reported a significant correlation between cTnT values and LA diameter and E/Ea septal. In agreement with these studies, our multivariate analysis showed that LA area index and E/Ea septal were significantly correlated with hs-cTnT levels.

ECG-Holter monitoring plays a major role in the detection of ventricular tachyarrhythmias and risk stratification of asymptomatic or symptomatic patients with HCM in as much as the episodes of NSVT can identify patients at higher risk for sudden cardiac death [15]. Moreno et al. [10] did not find any significant association between NSVT and hs-cTnT levels. In our study, however, although there was a significant association between NSVT and hs-cTnT in univariate analysis, there was no significant association between these two values in the multivariate analysis.

We found no significant association between hs-cTnT levels and LVEF or AF rhythm. There was only a trend for the patients with AF rhythm to have elevated hs-cTnT values. Nonetheless, previous studies suggested a significant association between these variables and hs-cTnT levels [10,13,16]. This incompatibility could be due to the small number of patients with LV systolic dysfunction (7 patients) or AF rhythm (6 patients) in our population study.

Age was not associated significantly with cTn levels in some studies [10,13]. In contrast, we found a significant correlation between increased age in our HCM patients and hs-TnT levels. This association was also found in a recent study by Kubo et al. [16].

Kubo et al. [16] revealed that the hs-cTnT level was an independent predictor of cardiovascular events in patients with HCM. Of significant note, the authors also reported that higher levels of hs-cTnT values were associated with greater risk. These findings have magnified the importance of the measurement of hs-cTnT levels in patients with HCM in the prediction of the prognosis in these patients [16].

Information regarding the precise mechanism and pathology of elevation in serum cTnT is unresolved. A study by Hessel et al. showed stretch-related mechanism of cTn release mediated by integrin [17,18]. In heart failure, an increased myocardial wall stress and LV end-diastolic pressure has been suggested as a leading cause of decrease in the subendocardial perfusion, and increase the concentration of cTn [17,19]. There are several studies that have demonstrated reduced myocardial perfusion, insufficient hypoperfusion, and myocardial fibrosis in HCM patients by magnetic resonance imaging [16,20–26]. It seems that inappropriate hypertrophy of the myocardium and therefore discrepancy between myocardial demand and coronary arterial supply is the probable pathologic mechanism of myocyte injury and therefore hs-cTnT release in HCM patients [16].

The present study merits due attention on account of its utilizing hs-cTnT as a novel cardiac specific marker in HCM patients. Moreover, our results revealed stable serum hs-cTnT levels; this is an issue that was not addressed in previous studies. There are, however, limitations to our study, first and foremost among which are its small sample size and its cross-sectional design with their inherent disadvantages. Another drawback of significance is that our study was a single-center one. We would suggest that further studies be conducted in larger populations in order to determine definitely the clinical value and determinants of hs-cTnT.

Conclusion

The results of the current study, conducted on patients with HCM, demonstrated that hs-cTnT was stably elevated in a significant proportion of the study population. In addition, age, LA area index, maximum LV wall thickness, and E/Ea septal were identified as the independent determinants of elevated hs-cTnT in our patients with HCM. It seems that the hs-cTnT serum level can be introduced as a valuable marker of myocardial injury in HCM patients.

Conflict of interest

The authors report no conflict of interest.

References

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